Kinetic Analyses Guide the Therapeutic Decision in a Novel Form of Moderate Aromatic Acid Decarboxylase Deficiency

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Résumé en anglais	Background: Aromatic amino acid decarboxylase (AADC) deficiency is a rare autosomal recessive disorder resulting in a combined dopamine and serotonin deficiency. About 50% of the cases set in the neonatal period. Here, we report an atypical clinical presentation with moderate symptoms. Patient: At 10months old, the patient presented paroxysmal eye movements without seizures, and feeding difficulties which were attributed to gastroesophageal reflux. She was investigated at the age of 7years, because of orofacial dyspraxia, hypomimie, axial hypotonia and focal segmental dystonia, bilateral ptosis, without evidence for cognitive impairment. Results: HVA [110nM; (reference value (rv): 202–596)] and HIAA (12nM; rv: 87–366) decreased, OMD (520nM; rv: 5–60) and 5-HTP (56nM; rv: 2–16) increased in CSF. We confirmed the diagnosis of AADC deficiency because the activity in plasma was low: 4pmol/min/ml; rv: 16–137. The kinetic analysis revealed a sixfold increase in the apparent affinity for l-dopa (4.26mM; control=0.71), but the V max was unchanged (37.5pmol dopamine/min/ml; control=39.1), suggesting a modification in the substrate binding-site. Molecular analysis revealed two heterozygous mutations in the DDC gene: c1040G > A; pR347Q already described, and a novel mutation c478C > T, pR160W. Conclusion: (1) CSF neurotransmitters metabolites suggested a moderate AADC deficiency; (2) The initial velocity saturation curve for l-dopa displayed a cooperative ligand binding behavior, in keeping with the modifications of the three-dimensional structure, induced by the amino acid substitutions (3) The treatment combination of l-dopa with pyridoxine dramatically improved the quality of life, the fatigability, and the paroxysmal eye movements.

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